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Differential tinnitus-related neuroplastic alterations of cortical thickness and surface area

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Abstract

Structural neuroimaging techniques have been used to identify cortical and subcortical regions constituting the neuroarchitecture of tinnitus. One recent investigation used voxel-based morphometry (VBM) to analyze a sample of tinnitus patients (TI, n=257) [1]. A negative relationship between individual distress and cortical volume (CV) in bilateral auditory regions was observed. However, CV has meanwhile been identified as a neuroanatomical measurement that confounds genetically distinct neuroanatomical traits, namely cortical thickness (CT) and cortical surface area (CSA). We performed a re-analysis of the identical sample using the automated FreeSurfer surface-based morphometry (SBM) approach [2]. First, we replicated the negative correlation between tinnitus distress and bilateral supratemporal gray matter volume. Second, we observed a negative correlation for CSA in the left peri-auditory cortex and anterior insula. Furthermore, we noted a positive correlation between tinnitus duration and CT in the left peri-auditory cortex as well as a negative correlation in the subcallosal anterior cingulate, a region collated to the serotonergic circuit and germane to inhibitory functions.
In short, the results elucidate differential neuroanatomical alterations of CSA and CT for the two independent tinnitus-related psychological traits distress and duration. Beyond this, the study provides further evidence for the distinction and specific susceptibility of CSA and CT within the context of neuroplasticity of the human brain.

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Keywords: tinnitus, surface-based morphometry, neuroanatomy, cortical thickness, cortical surface area

1. Introduction

Tinnitus can be conceived as an auditory phantom perception of transient or permanent sound, noise, or ringing without any corresponding external sound source [3]. In Western industrialized countries with steadily aging populations and enhanced exposure to environmental noise, the number of individuals who suffer from tinnitus is substantial [4]. According to recent estimations, approximately 50 million people in the US and 70 million people in the European Union are affected by tinnitus [5]. Although previous research and treatment focused on the inner ear, it has since been widely accepted that tinnitus should not be considered as a sole dysfunction of the ear, even though tinnitus is usually preceded by and associated with substantial to minor or even hidden peripheral hearing loss [6, 7]. Instead, it has widely been agreed that tinnitus emanates from a perplexing network that includes the inner ear, the auditory pathway, and non-auditory brain areas [8, 9, 10, 11, 12].

In particular, as there is presently no effective medical or psychological therapy available to cure tinnitus, it is of the utmost importance to better understand the sensory and cognitive mechanisms that directly or indirectly may result in alterations of cortical architecture. Careful research of the circumstances and conditions under which these changes occur may help to answer a number of pertinent questions. One important issue relates to the heterogeneity of the TI population which may be subdivided into a number of various tinnitus subtypes [6, 13]. A relevant question in this context pertains to the role that one cardinal feature, namely emotional distress,[1] plays in tinnitus subtyping [16, 17, 18, 19]. Recent research has shown that there is a high variability among people with tinnitus in the degree to which they are emotionally affected by the chronic noise [20]. While some TI learn to ignore and to cope with the disturbing noise, others begin to develop symptoms of mental, psychological and emotional disorders. In the absence of any reasonable and appropriate coping strategies, these persons consider the permanent sound to be extremely detrimental [21]. It has been suggested that the neural thalamo-cortical circuit that maintains the phantom sound connects increasingly with attentional circuits, and that this neural loop, being further accelerated by aversive emotional attributions, is continuously updated, eventually becoming chronically established [8, 22]. Thus, chronic subjective tinnitus could be considered a disorder that results from the maladaption of several overlapping brain systems that bind together in a 'vicious cycle' guided by principles of neural learning mechanisms. A recent paper takes an alternate stance by describing parallel networks that may

[1] Emotional distress in TI is measured by a standard self-report questionnaire, the Tinnitus Questionnaire (TQ) [14, 15]

differentially contribute to the experience of auditory and emotive-related tinnitus symptoms [9]. According to this model, deprived sensory inflow following damage in the peripheral hearing system impedes inhibitory circuits in the central peri-auditory nervous system. Whether fronto-cingulate-insular circuits are able to tone down the excitation of the central auditory functioning may vary considerably between individuals. In highly distressed TI various prefrontal, insular, and anterior and posterior cingulate regions may be conceived as being key nodes in this network that maintains the tinnitus experience [23].

With the advent of neuroimaging techniques a considerable number of functional brain scan studies have been performed (for reviews, see [24, 25]). The number of studies that scrutinized the neuroanatomical changes in the brain structure of TI is smaller, but for the time being, the results are notably inconsistent and heterogeneous [26, 27, 28, 29, 30, 31, 32] (for a review, see [33]). The range of brain regions that appear to undergo structural changes either as a function or as a catalyst of chronic noise perception includes the supratemporal, the lateral (pre-)frontal cortex, medial frontal, cingulate, temporal, subcallosal and parietal cortex as well as a number of subcortical nuclei. In particular, bilateral peri-auditory regions in the superior temporal lobe [26, 27, 28] and subcortical areas that are considered as part of the (anatomically ill-defined) limbic system [29, 34] often show anatomical changes. However, to date, neither the direction of tinnitus-related changes (increase or decrease of neuroanatomical gray matter (GM)) is clear, nor is it clarified whether the changes in the neural architecture of distinct regions occur independently or are related. The substantial discrepancy between studies is confusing and makes the interpretation of the (sometimes conflicting) data problematic. The methodological impediments that may complicate the comparability of studies on structural neuroplasticity in tinnitus are small sample sizes, comorbid psychological problems, differences in TI's age of onset and duration, that is the interval between tinnitus onset and the time point of data acquisition. Furthermore, evidence for confined "structural abnormalities specifically related to tinnitus is sparse" [33, p. 119], and this fact makes it difficult to test specific anatomical hypotheses. The results obtained from studies that used the standard VBM approach [27, 28, 29, 30, 32, 1, 35] are difficult to reconcile due to their heterogeneity. Thus the question arises whether the inconsistency of available results may be related to methodological limitations of VBM measurements [33]. Certainly, VBM results are not straightforwardly comparable to the results of studies that applied a more innovative approach, namely 'surface-based morphometry' (SBM) in their investigations into the structural signature of tinnitus [34].

As Panizzon and colleagues [36] argued, cortical volume (CV) as measured by the VBM approach is approximately the product of cortical surface area (CSA) and cortical thickness (CT). Therefore, if these variables run in opposite directions, CV measurements could be confounded and tinnitus-related alterations might be obscured. Since that publication a number of investigations empirically disentangled CSA measurements from the quantification of thickness [37, 38, 39, 40, 41, 42, 43, 44, 45, 46]. Sustaining this view, Bermudez and colleagues demonstrated that the perisylvian brain anatomy of musicians varies

as a function of the particular measurement methodology being used (VBM vs. measurement of CT by SBM) [47]. These studies provide strong evidence that cortical thickness and surface may differ in their relationship to behavioral traits and hence may confound CV measurements.

With respect to all this heterogeneity in both the applied measurement techniques and the experimental operationalizations, it is advisable to proceed in small steps. Following suggestions by other scholars [33, 48], our approach favors the replication of findings across independent research groups, as well as structural imaging methods (i.e., VBM and SBM) to increase both confidence and credibility of results [34]. Hence, we decided to replicate a large sample of recently published data that was intended to measure tinnitus-related structural changes of the human cortex [1]. In this study, VBM was used to elucidate tinnitus-related structural alterations in a sample of only TI. According to the authors, tinnitus-related distress correlated negatively with CV in peri-auditory areas, namely Heschl's gyrus and the bilateral insula. This relationship remained stable even after correcting for age, sex, hearing loss, and further covariates.

We consider this set of data as the most suitable for a replication for several reasons. First, the sample size (n=257) is expected to elicit high statistical power and a reliable cross-sectional representation of various tinnitus-related psychopathological and neuroanatomical aspects. Second, the sample is clinically well-characterized. Third, we think that tinnitus-related distress may prove to be a revealing trait as the investigation of its variance in the TI population in correspondence with other behavioral, neurophysiological, structural and psychological parameters may form an ideal platform for the study of the perplexing pathophysiology of tinnitus beyond the otological and audiological aspects. Unlike Schecklmann and colleagues [1] we applied an established SBM approach, namely the Freesurfer software suite [49, 50], which allows for the disentanglement of CT from CSA, thus enabling a more differentiated and detailed picture of the relationship between tinnitus-induced anatomical changes and the tinnitus-related psychometric traits of distress and duration. By using this approach, we are in keeping with the suggestion of Scheckelmann and colleagues [1, p. 1068] who recommended "the use of rather individualized strategies such as Freesurfer".

In sum, the present study is primarily intended to be a replication of the work by Schecklmann and co-scholars [1] who analyzed a large and homogeneous sample of TI by means of the standardized VBM approach. For the current analyses we used the identical sample of individuals who suffer from chronic subjective tinnitus but vary in their individually experienced emotional distress as quantified by the Tinnitus Questionnaire (TQ) [14]. Akin to Schecklmann and colleagues, we expect to find a negative relationship between tinnitus-related distress and CV, at least in bilateral peri-auditory regions. Furthermore, we hypothesize that in our analysis the same pattern will be observed for CSA as this neuroanatomical trait has been found to correlate strongly with CV [38, 43]. Regarding tinnitus duration, we are not able to provide well-based hypotheses; however, we expect to find alterations of thickness, which is believed to be a reliable marker of pathology-related as well as lifespan neuroplasticity. At the very least, we

postulate that an analysis of CV, CSA, and CT will yield results showing differences in plastic changes when distress is compared to duration, as we consider these two measures to be unrelated aspects of chronic subjective tinnitus [16, 1].

2. Methods

2.1. Participants

We re-analyzed structural MRI data of 257 participants (73 female) who took part in the study of Schecklamm and co-scholars [1]. The mean age was 50 ± 12 (range 16-77). All participants had a diagnosis of subjective tinnitus. The participants underwent comprehensive otological and audiological tests. Hearing function was defined as the mean threshold, and averaged over the frequencies 0.125, 0.250, 0.500, 1, 2, 3, 4, 6, and 8 kHz (left ear: 18 ± 15 (0-114) dB HL; right ear: 17 ± 13 (0-89) dB HL). The slope of the audiogram was taken into account by computing the hearing level difference of the pair of neighboring frequencies with the highest hearing level difference (left ear: 20 ± 12 (0-50) dB/octave; right ear: 19 ± 12 (0-70) dB/octave) [1].

We excluded patients who displayed hints of Ménière's disease, namely vertigo in combination with tinnitus, or who showed signs of objective, pulsatile tinnitus, that is a sound generated by a physical source, such as a vascular malformation. None of the patients reported any history of severe illness or exhibited contraindications for MRI scans (e.g., cardiac pacemakers or other implanted electronic devices, claustrophobia, etc.). All MRI scans were visually inspected. If there were artifacts or signs of brain malformation, patients were not included in the study. All participants gave their written, informed consent after a comprehensive introduction covering the experimental procedures. The study was approved by the Ethics Committee at the University of Regensburg. All procedures involved were conducted in accordance with the Declaration of Helsinki prior to the last revision in 2013 as the original data had been collected between 2004 and 2009.

2.2. Questionnaire

A German adaptation of the Tinnitus Questionnaire (TQ) was applied to assess tinnitus-related information [14]. TQ is a widely established instrument to assess tinnitus-related distress. It comprises 52 statements, which are judged on a three-point Likert scale ('true', 'partially true', 'not true'). The TQ has a factor structure that reveals the total score for tinnitus distress and severity, as well as six subscores ('Cognitive Distress', 'Emotional Distress', 'Intrusiveness', 'Auditory Perceptual Difficulties', 'Sleep Disturbances', and 'Somatic Complaints').

2.3. MRI data acquisition and analysis

2.3.1. MRI data acquisition

Magnetic resonance imaging (MRI) scans were acquired using a Siemens Sonata scanner at 1.5T and a standard 8-channel birdcage head coil. A 3 dimensional structural MRI was acquired for each participant using a T1-weighted magnetization rapid gradient echo sequence (time of repetition 1880 ms; echo time 3.42 ms; time to inversion 1100 ms; flip angle 15° ; matrix size 256x256), which yielded 76 sagittal slices with a defined voxel size of 1x1x1 mm. The scanner was upgraded twice within the measurement interval of five years (2004-2009). Consequently, an analysis of covariance was done to statistically control for this potential confound.

2.3.2. Surface-based morphometry

The reconstructions of cortical surface and volumetric segmentation were performed with the concurrent FreeSurfer image analysis suite (version 5.3.0). This software is documented online and freely available for download *(http://freesurfer.net)*. The technical details of these procedures are described in prior publications [49, 50, 51, 52, 53, 54, 55]. In short, the FreeSurfer pipeline generates models of the individual cortical surface with sub-voxel/-millimeter precision, yielding measures of CT, CSA and CV at each vertex of the surface. The fully automated procedure involves preprocessing of the subject's image data, segmentation of the cortical white and gray matter (GM/WM), tessellation of the GM/WM junction, inflation of the folded surface tessellation patterns, and automatic correction of topological defects. Notably, the procedures for measuring CT have been validated against both histological analysis [56] and manual measurements [57, 58, 59], and have been shown to be reliable [60].

For the statistical analysis, each participant's reconstructed brain was morphed to an average spherical surface and smoothed using a FWHM kernel of 10 mm as applied in previous work [34].

CT is defined by the shortest distance between the gray/white matter border and pial surfaces, while CSA is the mean area of the triangular region at the respective surface data point (vertex). Approximately, CV is the arithmetic product of CSA by CT. Indexes of gyrification at each vertex, as an added explaining factor for differences in volume, were also taken into consideration.

In addition, the cerebral cortex was parcellated into units based on gyral and sulcal structure, thus enabling the respective ROI statistics [61, 62, 63]. All subjects were analyzed on a Sun Microsystems HPC cluster running Linux SLES11 SP1. A visual inspection was performed randomly on selected subjects. At no time were the results manually edited.

2.3.3. Statistical analysis

To ensure an optimal comparability to the previous VBM analyses, whole-brain analyses using the built-in GLM of FreeSurfer were computed. Akin to the

study of Schecklmann and co-workers [1] the following steps of data analysis were performed: To start, we used tinnitus distress as measured by TQ as a single regressor in a principal model that does not specifically consider possible confounds. This model will be termed 'model without covariates' (MOC) throughout the remainder of this manuscript. To follow, a model with covariates (MWC) investigating the role of the cardinal nuisance factors, namely age, sex, hearing level [33], and further factors such as tinnitus duration, laterality, audiometric slope and scanner upgrade [1] was calculated.

This particular strategy was carefully deployed and evaluated in accordance with the previous work of Schecklmann and colleagues [1, p. 1064], as covariates can engender or annihilate statistical effects [64]. For the statistical analysis of both models, we used a significance threshold of 0.001 at vertex level analogously to the previous VBM analysis and a recent study by Vanneste and co-authors [35]. Both models were corrected for multiple comparisons for each hemisphere independently (FDR, $p < 0.05$ and Monte Carlo Null-Z simulation with an initial vertex-threshold of $p = 0.001$ and a cluster threshold of $p = 0.05$). We also report standard statistics without any correction with a threshold of 0.001 at vertex level.

Further to this, we applied a multiple regression analysis (MWC) in SPSS 21 (SPSS Inc., Chicago, IL) in order to conduct anatomical ROI analyses of the bilateral primary auditory cortices (AC) using the cortical parcellations of FreeSurfer [61]. The AC ROI was defined as being the bilateral transverse temporal gyrus (Heschl's gyrus) by the atlas of [61], which serves as the reference for the nomenclature of brain regions presented in Tables 1-6. Bonferroni adjustment was applied to control for multiple comparisons on the selected ROIs.

Finally, we used the volumetric estimates of subcortical structures independent of the cortical surface reconstruction stream within the FreeSurfer pipeline in an additional exploratory ROI analysis. ROIs related to the auditory system or tinnitus (models) were chosen out of the available subcortical structures, which resulted in a set including bilateral amygdala [12], hippocampus [29], nucleus accumbens [12], and thalamus [32]. The uncorrected results and Bonferroni-adjusted p-values are indicated in Table 7.

3. Results

Comprehensive demographic and tinnitus characteristics of the TI have been indicated by Schecklmann and collaborators [1]. The cortical reconstruction pipeline failed for one participant, leaving n=256 cases for further analysis. All other results of our SBM analysis are plotted in Figures 1-5 and Tables 1-7, and are described in the following paragraphs. Regarding the psychometric results, it is noteworthy that tinnitus distress as measured by the TQ total score and tinnitus duration do not correlate ($rho = 0.059$, $p = 0.345$).

The description of our anatomical results is organized according to the following structure: We start by delineating the findings for distress, and then follow these with the results for duration for each of the cortical parameters, namely volume, surface area, and thickness, respectively (Tables 1-6).

The analysis of the correlation between CV and distress in TI was intended to replicate the negative relationship observed by Schecklmann and co-authors [1]. Tables 1 and 2 list a comprehensive overview of the results for the correlations between CV and tinnitus distress. Notably, the analysis according to the MOC yielded a similarly weak effect (left AC $r = -0.284$, $p < 0.001$, right AC $r = -0.25$, $p < 0.001$) for the resulting clusters with the volume inversely related to tinnitus distress in both the left and the right auditory cortex situated on the supratemporal plane (cf. Table 3 of [1]). The comparable peak vertices are indicated by the green crosshairs (Figure 1).

– Please insert figures 1-5 and tables 1-6 near here –

When specifically addressing CSA the following pattern is remarkable (cf. Figure 2). We observed a negative correlation in the left auditory cortex ($-log10(p) = -3.30$, $r = -0.229$, $p < 0.001$, number of vertices (NOV) = 107, MNI = -47 -25 8) whereas the analysis of CT did not yield any significant results in this region. According to the whole-brain analyses, the effect was only significant in the left auditory area.

Tables 3 and 4 show that other regions also reveal a significant negative relationship between CSA and distress in distinct bilateral areas of the cortex, these being a lateral occipital region, an inferior parietal region, a superior frontal region, the unilateral right medial plane (cuneus), as well as the medial plane with anterior/posterior cingulate cortex.

Regarding CT, we found positive correlations for the medial plane, namely for the left and right medially situated posterior cingulate (Figure 3, Table 6). Apart from the correlations in PCC, thickness did not yield any significant positive correlations at the thresholded p-value (0.001), and only one negative correlation in the anterior superior temporal region (Table 6).

In line with our predictions, the additional multiple regression analysis on the anatomical ROI mean values controlling for all confounds (MWC) showed a significant negative correlation between tinnitus distress and neuroanatomical traits in the left core auditory ROI for both CV ($r = -0.149$, $p = 0.024$ (Bonferroni-adjusted) and CSA ($r = -0.151$, $p = 0.018$), whereas no significant

effect was found for CT ($r = -0.063$, $p = 0.608$) (Figure 4). In the right hemisphere, the pattern of results for the MWC model differs slightly, as we found no significant negative relationship for tinnitus distress and neuroanatomical parameters for all three traits, namely for CV ($r = -0.066$, $p = 0.544$), CSA ($r = -0.046$, $p = 0.446$), and CT ($r = -0.039$, $p = 1.054$). No significant correlations between tinnitus distress and gyrification indexes were found ($p < 0.001$). For tinnitus duration we observed significant effects in two regions, and only for thickness (Figure 5). We observed a negative correlation between duration and CT in the subcallosal anterior cingulate adjacent to the ventral striatum ($-log10(p) = -3.75$, $r = -0.251$, $p < 0.001$, NOV = 103, MNI -6 30 -5) and a positive relationship between duration and CT in the right anterior superior temporal lobe (covering the lateral convexity of the superior temporal gyrus (STG) and the dorsal banks of the superior temporal sulcus (STS)) ($-log10(p) = 4.25$, $r = 0.238$, $p < 0.0001$, NOV = 263, MNI = -51 -14 -11). It is noteworthy that no significant correlations of CSA and CV with duration were found (MWC, $p < 0.001$). It should be highlighted that tinnitus distress and duration were mutually controlled for by including them as covariates in the respective GLM models of the FS whole-brain analysis as well as the multiple regression analysis. The duration-CT findings reported in this manuscript are clearly distinct from the patterns of the distress-CSA correlations. As a final point, no significant correlations between tinnitus duration and gyrification indexes were found ($p < 0.001$).

For the sake of completeness, Table 7 indicates the results of the multiple regression analysis on the subcortical ROI volumes with tinnitus distress and duration. Notably, the volume of the left thalamus is weakly negatively correlated with tinnitus distress ($r = -0.128$, $p = 0.009$, uncorrected) whereas the left amygdala is positively correlated with tinnitus duration ($r = 0.110$, $p = 0.047$, uncorrected).

In sum, our SBM analysis revealed several specific relationships between tinnitus related behavioral indications (distress, duration) and neuroanatomical traits (CV, CSA, CT). More important, we replicated the negative relationship between individual distress and cortical volume in bilateral auditory fields that had formerly been revealed by VBM analysis [1]. Our analysis, however, also provides an additional value; regarding CSA and CT (which were not analyzed by the former VBM study) we observe a differential pattern of negative and positive correlations with distress and duration in the same sample of TI.

4. Discussion

In this section we begin by contrasting the pros and cons of the evaluated procedures for measuring cortical traits. To follow, we discuss our findings of differential patterns of neuroanatomical changes in tinnitus dependent on our primary variables, namely distress and duration, in the context provided by present knowledge on neural networks that bind together sensation, emotion, and cognition. However, we would like to concede that any interpretation of our CSA and CT findings are constrained by the moderate level of statistical confidence. Furthermore, akin to the previous VBM analysis [1], an uncorrected statistical threshold of $p < 0.001$ for the MWC model was deemed feasible due to a lower number of degrees of freedom. Finally, we address the potential limitations and conclude the article with general remarks.

Based on an automated surface-based morphometry approach, the present study delineates neurostructural changes in the brains of individuals suffering from chronic tinnitus. One of the major aims of the study was to test to what extent the SBM approach might provide more nuanced results than the VBM approach. For this reason we re-analyzed the same sample of individuals that had already been analyzed using VBM previously [1]. While we were able to replicate the changes in bilateral superior temporal cortical volume as already observed by Schecklmann and colleagues, we also demonstrate that the SBM approach enables a more differentiated insight, because it not only allows for the consideration of volume, but also that of the cortical thickness and surface area. Due to this disentangling, we were able to find correlations (uncorrected) that are indicative of distinct relationships in TI between distress and CSA, and duration and CT, respectively.

However, despite the fact that the architecture of SBM makes it possible to investigate more neuroanatomical traits than just CV, the results that it engenders are statistically less reliable. This may be due to the complex interaction of variables in the MWC model with the cortical parameters of CT and CSA, and the mentioned lowered number of degrees of freedom. A competent scholar should be aware of this shortcoming when interpreting the uncorrected data with a threshold of $p < 0.001$, which is not uncommon, as can be seen in the former analysis in the case of the MWC model [1], and in similar recent studies [35].

As indicated by our analysis, CSA and CT can be partly conceived as being distinct traits, and thus their analysis provides more nuanced information than the sole computation of CV as implemented in VBM. Given this understanding, the present study concurs with a pool of recent reports which also demonstrated the genetically and phenotypically distinctiveness of CT and CSA [38, 39, 41, 40, 42, 43, 65, 44, 45, 46]. It is important to mention that CV cannot be interpreted as a simple compilation of CT and CSA. With respect to the present study, we suggest a specific understanding of 'distinctiveness' in that there are variations in CSA that relate to distress and (also not) to duration while there are other variations in CT that may also give an account of the measured psychological traits. However, it is important to note that the different

variations in CT and CSA do not pertain to the same or overlapping variance in behavior. Accordingly, [66, p. 1141] concluded that "GM volume, which is a composite of 2 other traits (surface area and thickness), might not be the best choice". Even though recent clinical studies [27, 28, 31, 13, 35] continue to use VBM to identify apparent tinnitus-related group differences, we suggest that surface-based morphometry should be used in complement with VBM because it allows for the computation of three distinct parameters, namely CV, CSA, and CT. Thus, SBM minimizes the risk of underestimating or ignoring existing relationships between CT or CSA and behavior. Hence, the analysis of local differences (in cross-sectional approaches) or changes (in longitudinal approaches) in cortical volume (the arithmetical product of CSA and CT), surface area (the ratio of CV/CT), and thickness (the ratio of CV/CSA) may help to excavate subtle, informative patterns in complex data.

In the context of the comparison between the VBM and the SBM analyses of the same sample of TI, we conclude that our results *prima facie* replicate the outcome of Schecklmann and colleagues in that we also revealed a negative relationship between tinnitus distress and CV in bilateral supratemporal peri-auditory cortical fields. However, more specific, separate analyses of CSA and CT show that a different pattern for those distinct traits can be found in the midportion of the left supratemporal plane, while the less reliable effects in the right temporal lobe are not situated in Heschl's gyrus and, hence, cannot be considered as homologues to the cluster in the left STG (see Figure 2). This discrepant finding regarding the hemispheres was also observed in the VBM analysis [1].

Further into the analysis, we noted a negative relationship between distress and CSA, which means that TI who indicated a higher level of tinnitus-related emotional distress showed a systematically smaller surface of auditory-related cortex. Intuitively, one would expect such a relationship between behavior and CT, as the latter is understood to be a neuroanatomical trait that reflects neuroplastic alterations following enhanced sensory stimulation and experience. The finding that emotional distress, elicited by the sensation of chronic noise, is considerably stronger in individuals who demonstrate a smaller extent of CSA in the core auditory and adjacent insular regions, requires a compelling explanation. The anticorrelation between CSA and distress can be interpreted to imply that CSA, under some circumstances, is sensitive to plastic alterations and may decrease locally. However, with respect to the widely accepted 'radial unit hypothesis' this interpretation is implausible [67]. According to this framework CSA and CT have different origins. While CSA increases during late fetal development due to cortical folding, CT alters dynamically across the entire lifespan as a consequence of training, experience, and disease. By all means, the 'radial unit hypothesis' postulates that changes in CSA and in CT are not causally related to each other; any changes observed in CSA and CT are presumed to reflect different neuronal alterations [68]. Following the assumptions of this hypothesis, one would expect to observe stronger changes in CT of TI relative to CSA, the size of which has been considered to be more static. Alternatively, one may reason that the observed alterations of CSA are not a

consequence of tinnitus, but rather reflect a predisposition. A smaller CSA of core auditory and insular regions may predispose increased levels of tinnitus severity. This could be due to a limited cortical capacity for compensation of peripheral hearing loss or general inhibitory functions. A similar observation was made by Schneider and co-authors [69] who investigated the volumetric size of the core auditory regions in TI and CO by means of an in-vivo morphometry study. According to their findings, a reduction of cortical volume in auditory fields might be indicative of a higher predisposition for tinnitus. Even though our result is not this intuitively straightforward to interpret, we consider it to be of value as it provides interesting, additional evidence to the present debate about the roles of CT and CSA in pathology-related neuroplastic alterations. Longitudinal studies would be needed to answer the question whether the observed changes reflect predisposition or consequence of tinnitus, and to reveal the involved mechanisms. This is not a trivial issue as the results of current and recent functional and structural brain imaging studies are inconsistent regarding the functional or structural changes in the auditory cortex related to tinnitus [33]. While one recent study reported an increase in GM in the left primary auditory cortex of tinnitus patients [27], other studies observed a volume decrease in auditory regions [26, 1, 69]. To account for these differences it is reasonable to consider the role of duration as in our data we find differential neuroplastic alterations in the left auditory regions for distress and duration. Tinnitus duration is positively correlated with CT in adjacent portions of the temporal lobe whereas tinnitus distress is anticorrelated to CV and CSA in auditory regions. To overcome the unsatisfactory condition of inconsistency between different tinnitus-related studies, we consider it of the utmost importance to perform careful analyses on existing datasets in order to confirm previous results with differential analysis techniques, rather than the collecting and analyzing of new data. The present study should be considered a convenient example towards the realization of this strategy, and it is in line with concurrent efforts and suggestions forwarded by globally operating initiatives such as TINNET (http://tinnet.tinnitusresearch.net/).

We were not surprised to notice a relationship between distress and insular morphology as this sub-sylvian area can be conceived as an interface between the auditory system [70, 71] and the emotional brain circuitry [72] in the human brain. Along the same lines, Leaver and coworkers [34] observed a positive relationship between tinnitus distress and CT in the left anterior insula. Despite the fact that we report uncorrected results, we think it is appropriate to discuss our findings in light of present knowledge, as other scholars have also established a tight link between tinnitus and the insular region [34, 73, 74]. With reference to the tinnitus network, the insula has frequently been nominated as a key component due to its unique positioning, which facilitates integration across multiple domains including social, emotional, and attentional systems [37]. According to Nieuwenhuys and colleagues [75], the anterior insula subserves a multitude of functions, including the perception of pain and introspection about feelings. Other authors emphasize the involvement of the anterior insula in a network that is related to salience detection [76]. In conjunction with the ACC, the an-

terior insula "forms the core of a salience network that facilitates the detection of important environmental stimuli" [77, p. 663] and thus can be conceived as an "integral hub in mediating dynamic interactions between other large-scale brain networks involved in externally oriented attention and internally oriented or self-related cognition" [77, p. 655]. Furthermore, the tandem of anterior insula and ACC "integrate[s] bottom-up attention switching with top-down control and biasing of sensory input" [77, p. 663]. Given all this evidence, it is plausible that the observed subtle correlation between morphological alterations of the anterior cingulate-insular circuit and tinnitus distress may reflect an inappropriate evaluation of internally generated sounds and detrimental loss of inhibitory attentional control.

For the relationship between CT and distress, we observed a positive correlation (uncorrected) in the bilateral posterior cingulate while CSA was negatively correlated (uncorrected). A similar relationship was not observed by Schecklmann and colleagues [1] and can thus be considered an additional value of our SBM analysis. It is an example of a 'canceling-out' effect in CV as CT and CSA are both positively and negatively correlated with distress in the same region, and therefore changes in CV may not be discernible. Furthermore, the findings at this site are in accordance with the predictions based on the 'radial unit hypothesis' in that CT is typically regarded as a neuroanatomical trait that may increase or decrease as a function of lifespan development and disease. In the context of the present pattern of results, this finding indicates that an increase in distress may result in an increase of the synaptic connectivity and neuronal density (CT) in the posterior cingulate cortex, whereas the smaller CSA could be an underlying predisposition for this change in CT. Even though our reasoning is based on uncorrected results, we consider it relevant to report both the results and the reasoning, because they provide support for current models of tinnitus circuits in the human brain. In line with the framework described by De Ridder and coauthors [9], the posterior cingulate cortex is a node of the large-scale neural network that represents tinnitus-related distress. Jastreboff [78] located memory-related functions in the context of tinnitus to the posterior cingulate. With respect to the proposal by De Ridder and colleagues [8] these results can be easily reconciled. Accordingly, tinnitus emerges as a function of several large-scale networks that bind together various aspects of perception, salience, memory, distress, and audition. The cingulate cortex appears to play a key role in these large scale networks as we observed both increases and decreases of CT and CSA in distinct portions of the cingulate cortex with tinnitus distress.

In addition, we analyzed the relationship between duration and changes in CT and CSA, respectively. Notably, a recent study that combined EEG with VBM analyses in a large sample of TI [35] failed to discover any relationship between CV and duration (even though they applied the same vertex/voxel-wise significance threshold that we used in our analysis). While in our sample no effects were observed for CSA, we did find two significant effects for CT (uncorrected). The first effect is an anticorrelation between CT in the subgenual anterior cingulate cortex (see Figure 5). This indicates that the longer the duration of

tinnitus, the stronger the morphological reduction in this region (or vice versa). Interestingly, two recent frameworks consider this region to be of key importance in the pathophysiology of tinnitus. According to the 'phantom pain' model by De Ridder and colleagues [8], "the subgenual anterior cingulate cortex mediates an overlap (or hub) with a central autonomic control system" [33, p. 123]. Furthermore, Vanneste and colleagues [19, p. 478] linked the subcallosal anterior cingulate cortex to a circuit that is part of a "common emotional and attentional distress network". However, our analysis provided no evidence for a link between the subcallosal area and tinnitus-related distress.

It is our view that the 'gating' model by Rauschecker and colleagues [12] provides an alternate and more plausible explanation. According to this model, tinnitus is the result of a dysfunction in a cortical-subcallosal-thalamic loop. In non-affected individuals this circuit functions as a system that tones down unwanted auditory noise, in that serotonergic neuronal ensembles in the subcallosal ventral striatum modulate the function of the thalamic reticular nucleus (TRN). The TRN is meant to inhibit the auditory thalamus and, in so doing, to block the aversive sound from encountering the auditory cortex. In the terminology of Rauschecker and colleagues [12] the mechanism can be termed a 'tuning out' device that filters out the tinnitus signal. The model further proposes that in TI the integrity of the subcallosal circuit is disrupted, in which case the inhibiting projections of the TRN to the auditory thalamus are attenuated, and hence the tinnitus percept is relayed to the auditory cortex without hindrance. According to this model, anomalies within this limbic-cortico-striatal-thalamic loop result in deviant processing of the tinnitus sound. Due to the gating mechanism breaking down, the inhibitory device that is part of a normal noise canceling system does not work properly. Rauschecker et al. [12, p. 823] propose that the "inhibition of the tinnitus signal at the thalamic gate is lost". As such the persistent sound becomes salient and "leads to permanent reorganization and chronic tinnitus" [12, p. 823]. It is plausible to reason that a steadily progressive long-term thinning of the subcallosal area fosters the establishment of this vicious cycle. Remarkably, our finding of an anticorrelation between duration and CT in the subcallosal area (even though it is based on uncorrected results) fully concurs with the concept that ongoing tinnitus may be related to progressive reorganistion of the subcallosal anterior cingulate, which is in line with the 'gating' model [12], but would require a modification of the 'phantom pain' model. A similar finding has been reported by Leaver et al. [34] who also applied the SBM approach to identify neuroanatomical markers of tinnitus. Notably, Leaver and colleagues obtained their results by comparing TI with controls who were matched for age and hearing loss. Although this makes it difficult to compare their results with the current findings, some observations merit discussion here. Similar to our results Leaver and co-authors also noted a decrease in CT in the subcallosal area. However, whereas Leaver and colleagues excavated a relationship between CT decrease and increased depression and anxiety scores, we observed a subcallosal decrease related to duration when data were corrected

for BDI ($-log10(p) = -3.37$, $p < 0.001$)[2]. We have therefore concluded that tinnitus duration is the sole factor, independent of any other factor, that results in a decrease of thickness in the subcallosal area.

A converse effect (i.e., an uncorrected positive correlation between CT and duration) was evident in the left anterior superior temporal lobe. The significant cluster covers a strip of cortical tissue at the lateral surface convexity of the STG, extending to the STS. This part of the human brain cannot be considered a part of the core tinnitus network in a strict sense, even though De Ridder and colleagues involve the left superior temporal lobe in their reasoning [9]. Based on a study by Brancucci and co-workers [80], De Ridder and colleagues mention that the bilateral middle temporal gyrus is part of a subnetwork that mediates the awareness of pitch. Elsewhere in the same paper, De Ridder and co-authors discuss the left anterior STS as being a part of a subnetwork that serves self-perceptional functions. They reason that awareness and self-perception are densely intertwined. Hence, the self-perception network (in connection with the salience network involving the anterior insula and the dorsal anterior cingulate cortex) "most likely has to be activated for the tinnitus to be consciously perceived" [9, p. 20]. We favorably interpret the CT increase in the left anterior STG/STS as a plastic effect that may have resulted from the increased awareness and self-perception in TI.

Interestingly, the Freesurfer analysis also revealed alteration in subcortical structures even though the software is optimized for cortical surface measurements. For this reason we are reluctant to interpret these findings. However, the subcortical nuclei, namely the thalamus and the amygdala, have also already been located roles in tinnitus-related networks [9]. Regarding the thalamus, it is additionally worth mentioning that it is part of a triangle, consisting of auditory cortex, insula and thalamic nuclei, that supports audition in general [81].

General remarks and limitations

Our reasoning may help to capture innovative aspects of the causal interplay between observed neuroanatomical changes and behavioral patterns in a large sample of TI. Although some of our conclusions are based on uncorrected results, we consider it relevant to report them transparently, because they can be seen as pieces of a mosaic that either provide evidence for or against the current frameworks of tinnitus generation and maintenance. In addition to the major results reported and discussed above, several minor issues that might be of interest are communicated in the following.

One objection may be that the current study does not involve a control group that consists of individuals without symptoms of tinnitus. First, our aim was to replicate and to extend the results reported by Schecklmann and coworkers. Their previous study did not include a control group either. Second, we focused on the relationship between tinnitus-related behavioral parameters, namely distress and duration, and neuroanatomical alterations. Recent studies comparing

[2]In our sample Beck Depression Inventory data (BDI, [79]) for 154 patients are available

neuroanatomical differences between TI and normal controls reported inconsistent results. We think that the considerable variance within the samples of TI accounts for these partly contradictory findings. For this reason we refrained from adding a group of controls. Furthermore and with respect to future studies, we advocate a change in tinnitus research paradigms in that we propose that the various facets of tinnitus should primarily be investigated within large samples of TI rather than contrasting TI with non-affected controls.

Another question may be why we did not observe a relationship between neuroanatomical changes and hearing loss. Again, we would like to emphasize that the statistical models we applied in the analysis were controlled for hearing loss. The same holds for the lateralization of tinnitus.

Current and recent functional and structural brain imaging studies are inconsistent pertaining to the relationship between self-reported tinnitus laterality and functional or structural changes in the auditory cortex [69]. In the present study, the majority of TI indicated a bilateral tinnitus experience (n=182), which would suggest that bilateral neuroanatomical changes in this region would be found. However, we only noted a significant negative relationship between CSA and distress in the left, but not in the right, core auditory region in the ROI analysis (see Figure 3). At the very least, our data partly concur with the observations from a recent functional study [82], in that the tinnitus-related activation appears to be left-dominant (whereas activation in the right hemisphere is more wide-spread) and independent of self-reported tinnitus laterality. Akin to the study of Vanneste et al. [35], we did not obtain significant differences for neuroanatomical measurements by contrasting unilaterally distributed (left vs. right) TI sub-samples. Regarding future studies, we recommend that the potential influence of hearing loss and tinnitus lateralization be considered when the study is designed in order to investigate specific hypotheses and respective contrast groups with a sufficient number of cases.

Our finding of a decrease in the subcallosal thickness related to tinnitus duration may be explained by the limited range of available audiometry. According to Melcher and co-authors [31], high-frequency hearing loss (>8KHz) but not tinnitus per se may account for reductions in subcallosal gray matter.

Naturally, a neuroanatomical examination that considers only gray matter traits is not complete. We agree that changes in white matter architecture can also be conceived as neuroplastic biomarkers of the tinnitus network [26, 83, 28]. As outlined by Adjamian and co-authors [33] these studies report both local increases and decreases of white matter fiber tracts in TI. However, it cannot be ruled out that this "evidence more consistently suggests that hearing loss induces white matter alterations, and when taking this into account differences related to tinnitus prove debatable" [33, p. 129]. Unfortunately, diffusion-weighted imaging (DWI) recordings of our sample of TI are not available, and we are therefore not able to provide complementary evidence on altered white matter architecture.

Albeit that our study revealed that distinct cortical areas clearly vary systematically in surface or thickness as a function of tinnitus-related distress and duration, we lack the evidentiary basis from which to conceive these ensembles of areas as 'networks' in a strict sense. To learn more about the existence of

tinnitus-related neural subnetworks as delineated by DeRidder and et al. [9], it is not sufficient simply to expose distinct areas without a complementary analysis of effective structural connectivity. To this end, Golm and collaborators [18] raise the question of how tinnitus-specific a 'network' made up of a sample of typical candidate regions may indeed be?

Yet another question raised may be whether an increase or a decrease of CT should be considered advantageous or detrimental. Intuitively, it is reasonable that a thicker cortex would accommodate more neuronal packing and would allow for more computational resources, thus making it conceptually more proficient. However, the conclusion that a 'thicker' cortex can generally be considered a 'better' cortex is not sanctioned by the literature. The question as to what extent a 'thicker' cortex is 'better' can only be discussed when it is carefully embedded in the context around each study-specific dataset [43].

The important issue of direction of causality is often ignored in cross-sectional studies that seek to establish relationships between specific behavioral traits and neuromorphological changes. According to the standard approach, it is assumed that increased distress or annoyance, which appears to be related to the occurrence and maintenance of tinnitus, causes structural changes in the tinnitus brain. However, one cannot rule out the opposite causal relationship in which smaller/larger brain regions cause the pathological behavior, namely tinnitus. Longitudinal studies are arguably the sole approach towards ending this debate.

Overall, like the previous VBM analysis [1] and indeed neuroanatomical studies on tinnitus in general, the statistical effects here are small and reported transparently. Furthermore, we refrained from reporting results which were not comparable with the statistical procedure of the former VBM analysis.

The reanalysis of a large sample of thoroughly investigated TI with an innovative approach is one beneficial aspect of the current study. Thus, we are able to directly compare the pros and cons of the two analysis techniques, while all other factors (scanning environment, participants' profiles and neuroanatomical heterogeneity) are strictly controlled. Based on comprehensive psychometric protocols of the participants involved in the two studies, a multitude of post-hoc computations are possible. With respect to future studies, the establishment of large databases, longitudinal designs, and the introduction of homogeneous procedures of data analysis should be considered both convenient and imperative. Furthermore, the combined use of functional/structural imaging techniques (MRI, diffusion weighted imaging, EEG/MEG) as recently published by Vanneste et al. [35] should be established as a second important line of development.

Conclusion

By applying an automatic standardized SBM data analysis approach, namely FreeSurfer, we were able to extend the results of a previous VBM study on the same sample of TI. In more detail, our approach identified specific relationships between behavioral tinnitus-related parameters and distinct neuroanatomical

traits, namely CT and CSA. Based on uncorrected results, we observed that tinnitus distress seems to be favorably related to a reduction in CSA, while tinnitus duration appears to correspond to changes in CT. Hence, SBM as compared to VBM seems to generate a wider array of results which may allow for a more nuanced insight into the subtle cortical neurodynamics of tinnitus.

Despite the recently expressed reservations on the present progress of our understanding of the relationship between tinnitus and gray matter alterations [33, 48], we consider the present study to be a valuable and necessary contribution towards reconciling recent technical and methodological advancements.

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					MNI				
	Annotation	Max	NVts	Size (mm2)	X	Y	Z	NVts FDR	CWP MCZ
LH									
	transverse temporal	-5.42	888	408.44	-51	-21	4	74	0.0007
	inferior temporal	-4.27	111	63.52	-44	-50	-12		
	rostral middle frontal	-4.11	234	173.4	-20	56	-2		0.0473
	superior frontal	-3.67	195	102.13	-7	27	55		
	rostral middle frontal	-3.32	81	68.4	-23	54	16		
	superior frontal	-3.31	67	26.18	-7	52	36		
	superior temporal	-3.30	28	23.63	-48	9	-25		
	postcentral	-3.14	60	28.6	-32	-31	61		
RH									
	lateral orbitofrontal	-5.69	656	281.21	16	21	-17	486	0.0059
	inferior parietal	-4.58	378	171.66	45	-55	43	230	
	superior temporal	-4.30	228	101.31	59	-1	-4	114	
	parahippocampal	-4.11	122	49.09	37	-35	-15	56	
	insula	-3.91	175	80.31	36	3	1	67	
	cuneus	-3.72	151	120.41	5	-77	16	25	
	transverse temporal	-3.40	52	20.11	43	-24	3		
	rostral middle frontal	-3.27	33	20.17	37	51	9		
	rostral middle frontal	-3.23	84	59.9	16	21	-17		
	pars orbitalis	-3.20	32	26.06	45	-55	43		
	lateral orbitofrontal	-3.13	14	8.44	59	-1	-4		
	superior temporal	-3.08	17	6	37	-35	-15		

Table 1: Statistics of the negative correlations of cortical volume and tinnitus distress (MOC). Left hemisphere (LH): Max: -log10(p) at peak vertex (values > 3 correspond to $p < 0.001$), NVts: number of vertices above threshold ($p < 0.001$, uncorrected), NVts FDR: number of vertices above threshold ($p(FDR) < 0.000022$), CWP MCZ: cluster-wise p-value of Monte Carlo Null-z simulation (vertex-wise/initial $p = 0.001$). Right hemisphere (RH): $p(FDR) < 0.00029$.

					MNI		
	Annotation	Max	NVts	Size (mm2)	X	Y	Z
LH							
	inferior temporal	-4.45	113	124.04	-45	-50	-12
	rostral middle frontal	-3.29	29	95.66	-20	55	-3
	superior temporal	-3.07	7	70.18	-47	8	-26
RH							
	insula	-5.34	232	169.49	39	1	1
	inferior parietal	-3.48	137	315.75	44	-63	39
	inferior parietal	-3.39	65	114.12	43	-66	25
	inferior temporal	-3.31	28	69.94	55	-23	-24
	inferior parietal	-3.15	36	20.11	46	-56	44

Table 2: Statistics of the negative correlations of cortical volume and tinnitus distress in both hemispheres (MWC). Max: -log10(p) at peak vertex (values > 3 correspond to $p < 0.001$), NVts: number of vertices above threshold ($p < 0.001$, uncorrected).

					MNI		
	Annotation	Max	NVts	Size(mm2)	X	Y	Z
LH							
	superior frontal	-3.80	201	100.06	-7	28	54
	lateral occipital	-3.49	224	197.41	-20	-97	5
	fusiform	-3.46	129	71.42	-41	-49	-17
	transversetemporal	-3.30	107	41.61	-47	-25	8
RH							
	superior temporal	-4.61	314	127.32	64	-37	16
	lateral orbitofrontal	-3.05	12	8.27	15	46	-19

Table 3: Statistics of the negative correlations of cortical area and tinnitus distress in both hemispheres (MOC). LH: Left hemisphere, RH: Right hemisphere, Max: -log10(p) at peak vertex (values > 3 correspond to $p < 0.001$), NVts: number of vertices above threshold ($p < 0.001$, uncorrected).

					MNI		
	Annotation	Max	NVts	Size (mm2)	X	Y	Z
LH							
	fusiform	-3.56	79	38.31	-40	-46	-17
	lateral occipital	-3.26	57	35.82	-14	-99	13
	superior temporal	-3.12	30	14.78	-54	-26	1
	lateral orbitofrontal	-3.09	14	4.98	-28	24	2
	superior frontal	-3.05	7	4.07	-7	29	52
	posterior cingulate	-3.04	8	2.64	-11	-2	40
RH							
	lateral occipital	-3.30	86	74.52	30	-93	-1
	superior temporal	-3.28	83	30.81	64	-38	17
	inferiorparietal	-3.18	54	27.19	47	-62	35
	fusiform	-3.16	44	21.92	43	-51	-12
	medialorbitofrontal	-3.01	3	2.0	8	41	-11
	insula	-3.01	2	1.0	36	4	1

Table 4: Statistics of the negative correlations of cortical surface area and tinnitus distress in both hemispheres (MWC). LH: Left hemisphere, RH: Right hemisphere, Max: -log10(p) at peak vertex (values > 3 correspond to $p < 0.001$), NVts: number of vertices above threshold ($p < 0.001$, uncorrected).

					MNI		
	Annotation	Max	NVts	Size(mm2)	X	Y	Z
LH							
	superior temporal	-4.29	163	75.47	-47	-11	-13
	supramarginal	-4.24	107	43.58	-53	-32	37
	lingual	-4.11	99	65.72	-12	-71	3
	inferior parietal	-3.73	79	51.64	-39	-78	26
	middle temporal	-3.73	121	73.72	-61	-45	-7
	rostral middle frontal	-3.62	89	57.73	-23	42	32
	caudal middle frontal	-3.29	36	17.8	-35	4	32
	rostral middle frontal	-3.08	32	20.51	-33	49	7
RH							
	medial orbitofrontal	-3.76	60	32.82	10	22	-18
	lingual	-3.64	93	31.76	23	-51	0
	superior temporal	-3.56	114	71.68	57	-6	-9
	inferior parietal	-3.15	22	9.12	47	-54	45
	superior frontal	-3.02	4	3.46	11	55	12

Table 5: Statistics of the negative correlations of cortical thickness and tinnitus distress in both hemispheres (MOC). LH: Left hemisphere, RH: Right hemisphere, Max: -log10(p) at peak vertex (values > 3 correspond to $p < 0.001$), NVts: number of vertices above threshold ($p < 0.001$, uncorrected).

					MNI		
	Annotation	Max	NVts	Size (mm2)	X	Y	Z
LH							
	posterior cingulate	3.10	16	5.49	-4	-15	35
	superior temporal	-3.04	6	2.7	-47	-9	-13
RH							
	posterior cingulate	3.00	1	0.45	6	-7	40

Table 6: Statistics of the positive and negative correlations of cortical thickness and tinnitus distress in both hemispheres (MWC). LH: Left hemisphere, RH: Right hemisphere, Max: -log10(p) at peak vertex (values > 3 correspond to $p < 0.001$), NVts: number of vertices above threshold ($p < 0.001$, uncorrected).

	distress			duration		
	r	p-value	p-bonf	r	p-value	p-bonf
Left Amy	-.052	.347	1	0.11	.047	0.376
Left HC	-.047	.403	1	.015	.783	1
Left Nacc	-.074	.159	1	-.028	.593	1
Left Tha	-.128	.009	.072	.063	.2	1
Right Amy	-.061	.279	1	-.009	.872	1
Right HC	-.033	.565	1	.022	.697	1
Right Nacc	-.001	.989	1	-.008	.87	1
Right Tha	-.021	.688	1	.066	.203	1

Table 7: ROI analysis of subcortical structures: Correlations of tinnitus distress and duration with subcortical volumes as elicited with multiple regression analysis (MWC). Amy=Amygdala, HC=Hippocampus, Nacc=Nucleus accumbens, Tha=Thalamus, p-bonf= bonferroni-adjusted p-value.

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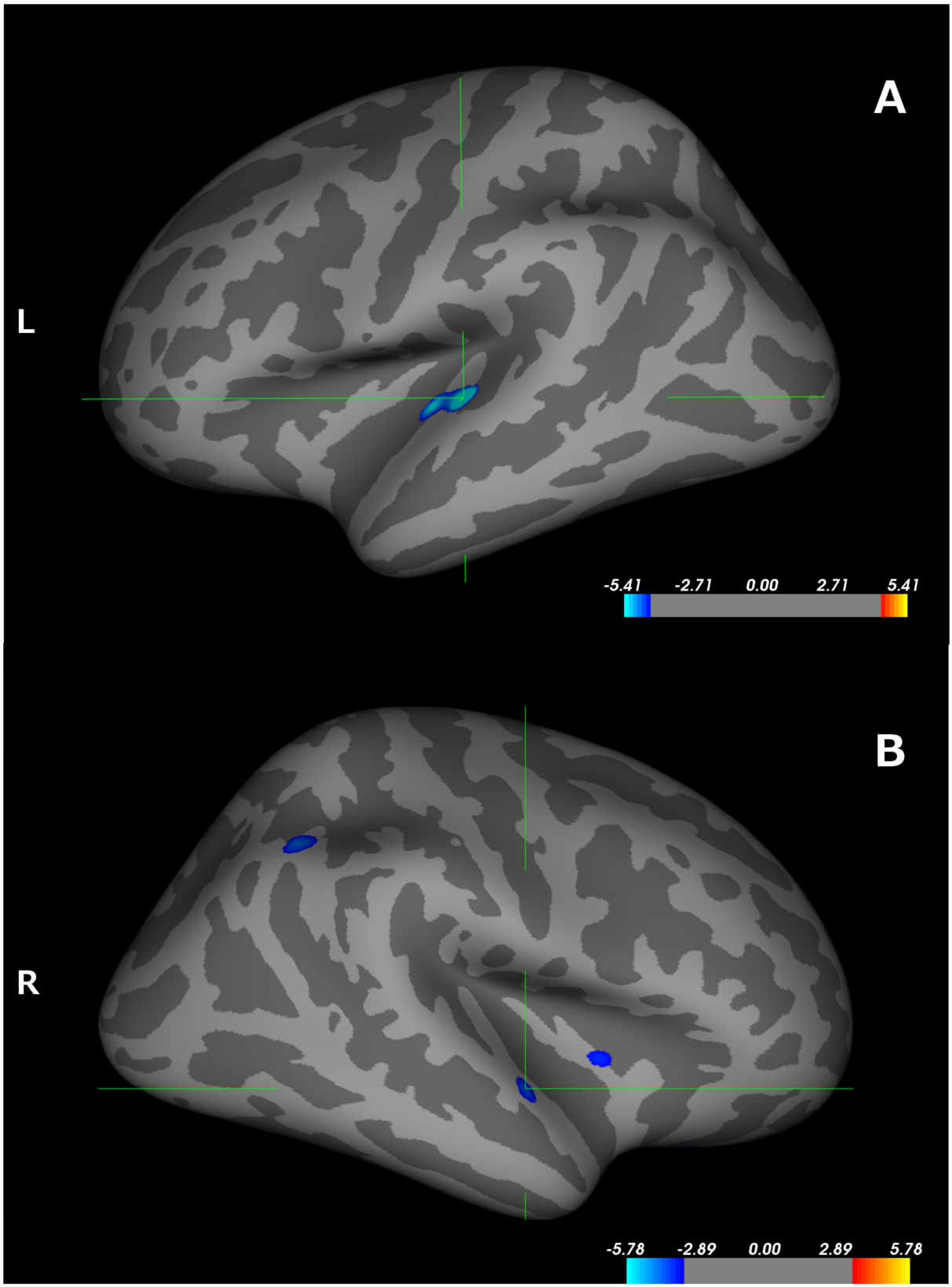
Figure 1: Negative correlations of tinnitus distress with CV in the left hemisphere (A) and the right hemisphere (B) of MOC. Green cross hairs indicate peak vertices (A: MNI -51 -21 4, B: MNI 59 -1 -4) comparable to peak voxels of VBM analysis (cf. figure 1 of [1]).

Figure 2: Negative correlation of tinnitus distress with CSA in the left AC (MOC. See tables 3 and 4 for more details.).

Figure 3: Correlations of tinnitus distress with CT (left panel) and CSA (right panel) in bilateral cingulate cortex (MWC, thresholded at p=0.005 for illustration. See tables 5 and 6 for more details.).

Figure 4: ROI analysis: Negative correlations of tinnitus distress with CV and CSA but not CT in the left transverse temporal gyrus as elicited by multiple regression (MWC). A: Partial regression plot of tinnitus distress vs. left transverse temporal gyrus cortical volume: r=-0.149, p=0.024* and right transverse temporal gyrus cortical volume: r=-0.066, p=0.544. B: Partial regression plot of tinnitus distress vs. left transverse temporal gyrus cortical surface area: r=-0.151, p=0.018* and right transverse temporal gyrus cortical surface area: r=-0.046, p=0.892. C: Partial regression plot of tinnitus distress vs. left transverse temporal gyrus cortical thickness: r=-0.063, p=0.608 and right transverse temporal gyrus cortical thickness: r=-0.039, p=1.054.

Figure 5: Correlations of tinnitus duration with CT in the left hemisphere (MWC). Left panel: positive correlation of tinnitus duration with CT in STS. Right panel: negative correlation of tinnitus duration with CT in sgACC.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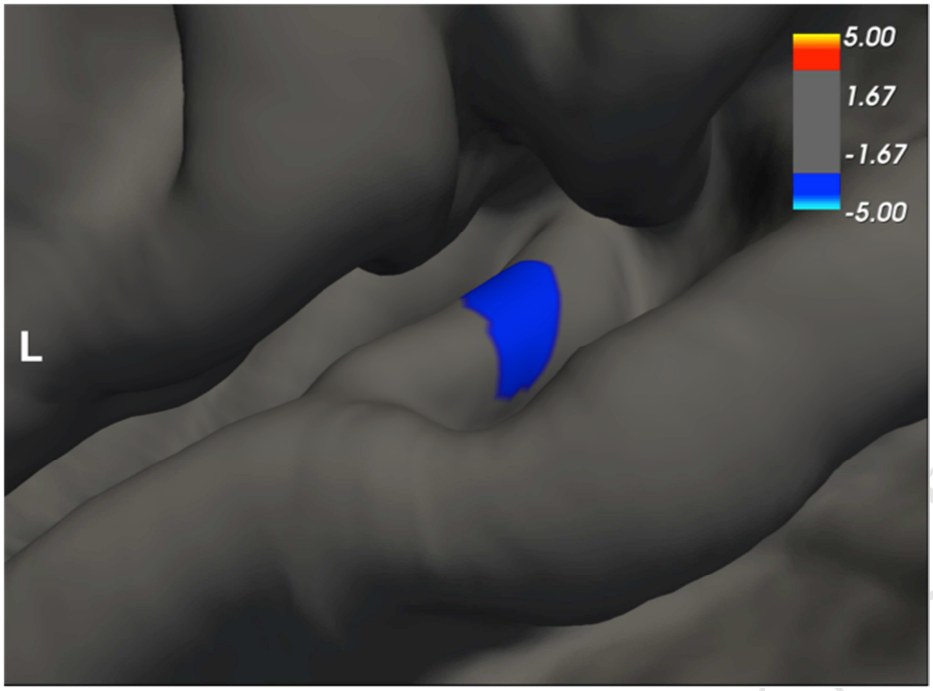

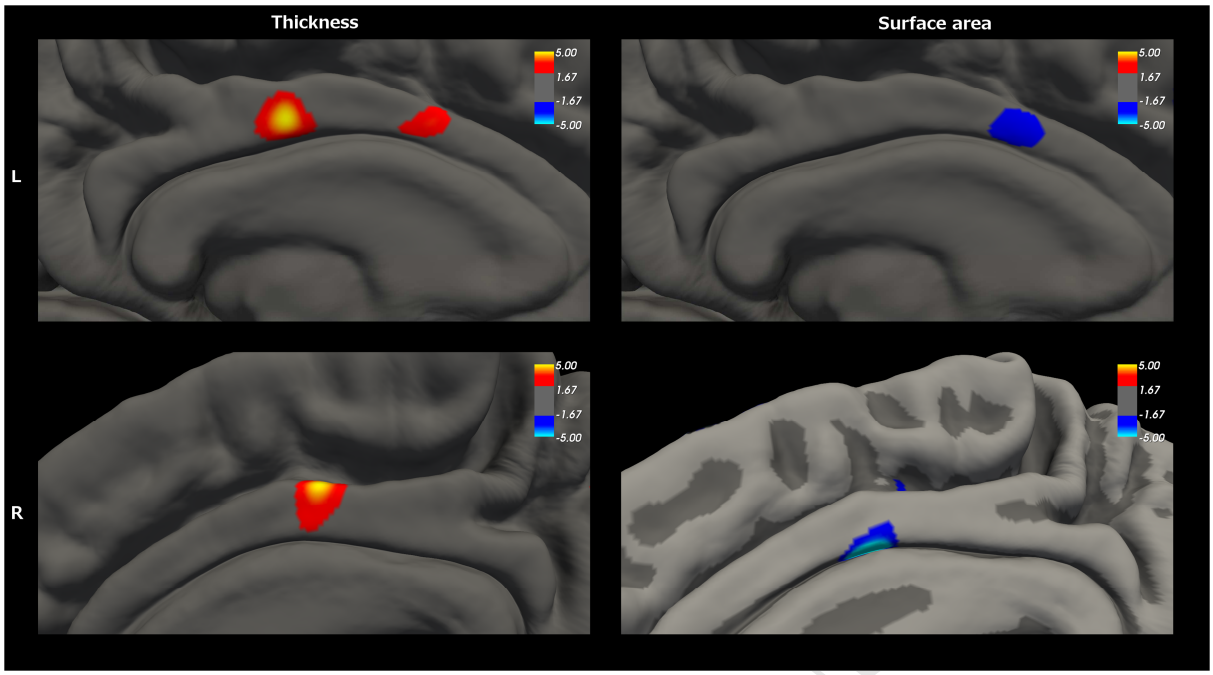

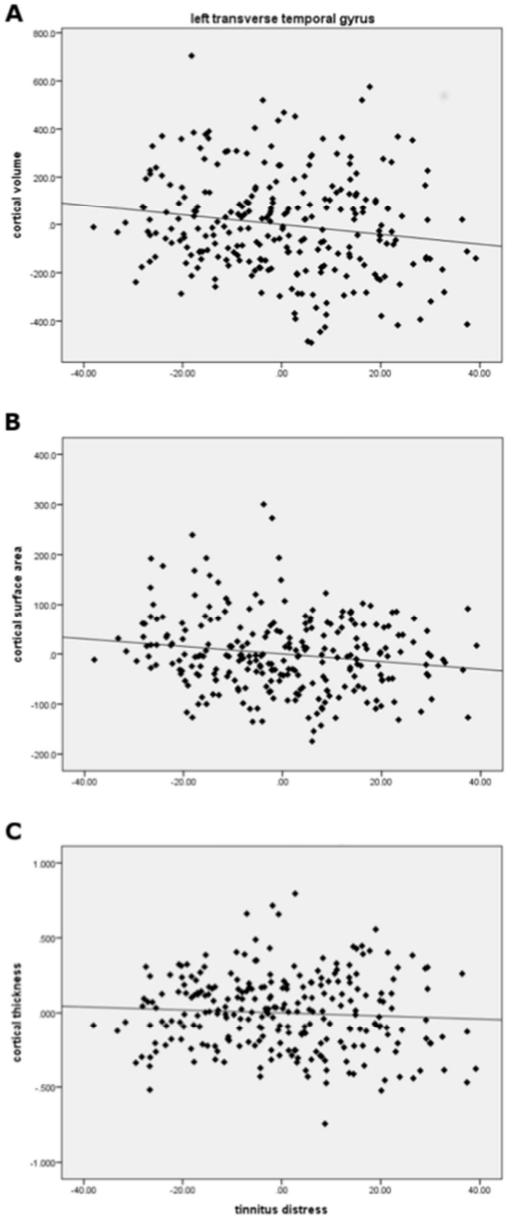

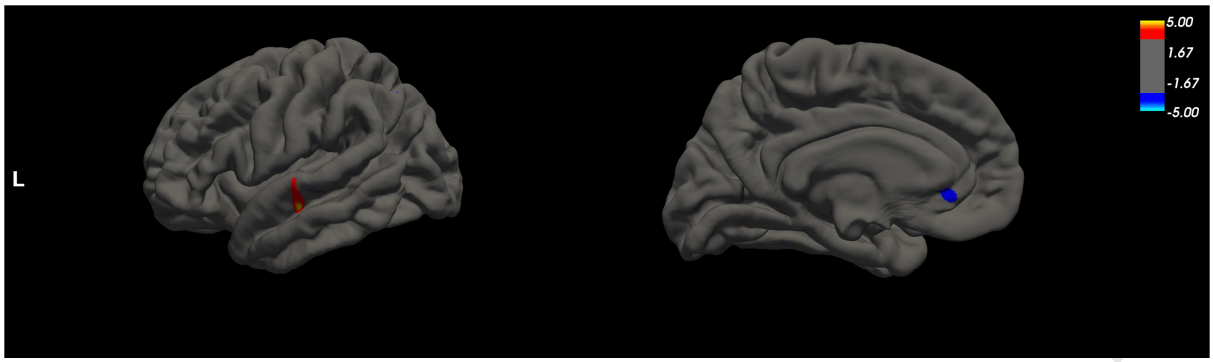

- Cortical thickness and surface area differentially correlate with tinnitus distress and duration
- Cortical thickness reductions in the subcallosal area correlate with duration of tinnitus
- Surface-based morphometry provides added value to the study of tinnitus-related neuroanatomical changes